Bandolier 59

What do we think?
What do we know?
What can we prove?

Evidence-based health care **£3.00** **January 1999 Volume 6 Issue 1**

This is ***Bandolier***'s now home. Yes, it is beautiful, and, yes, we are lucky that buildings like this can be produced without cost to the NHS or universities, as this one was. Thank you, Pain Research, for having us.

This month ***Bandolier*** follows up more readers' requests, this time to try and sort out treatments for acute migraine. There are so many new triptans, and many existing medicines, that a full-blown review of the area would take many people several months. ***Bandolier*** did what any ordinary professional may do - a quick search for systematic reviews, and wrote to the companies for information on RCTs. The result is a table of NNTs.

This month, ***Bandolier*** also reprises the calculation and use of NNTs, again by request. This time we have a four page pull out section (more like the Sunday Times each month) which includes a page of simple-to-follow instructions which can be used when you are faced with a paper or review you want to make sense of. In the insert, we use this page to show how NNTs for sumatriptan could be calculated, but on page 8 there is a clean version which can be copied and used in your practice. We'd love feedback.

Finally, on page 7 some of the Internet sites that ***Bandolier*** finds most useful are featured.

In this issue

MAKING SENSE OF MIGRAINE TREATMENTS?

New triptans are becoming available for the treatment of acute migraine headaches. How effective are these at relieving acute pain due to migraine? Is one better than the others? Are there alternatives? What should we do?

All these questions and others will, of course, be answered when the National Institute of Clinical Excellence starts cranking out the guidelines and guidance, and there will already be many local prescribing policies in use. But ***Bandolier*** wanted the answer ***now!*** One way of trying to find it was to do a "Saturday night special" review, using common entry criteria and common endpoints to try and see whether NNTs were about the same or very different, and to try to assess the weight of evidence for each possibility.

The trigger for this was a superb meta-analysis of sumatriptan [1] by Peer Tfelt-Hansen of Copenhagen. This review (of which more below) is a source of knowledge and wisdom about the conduct of migraine trials. Because sumatriptan is a modern medicine it has been subjected to many clinical trials of high quality, which makes for fertile ground for asking lots of different questions.

Strategy

Bandolier knows it is in a privileged position with regard to finding information, so the strategy was to approach the search much like an average GP connected to the Internet might do. We were looking for placebo-controlled RCTs of analgesics used for the treatment of acute migraine. We searched our own in-house databases (filing cabinet), PubMed for the last few years looking for meta-analysis and migraine, and wrote to companies requesting published randomised controlled trials of products already marketed.

To be included in the analysis, a trial had to be a single dose, randomised, double blind and placebo controlled comparison of a treatment for an acute migraine attack. If it was a multiple dose study we had to be able to extract single dose data. We were not interested (at this stage) in head-to-head comparisons of one antimigraine compound versus an active control.

All patients conformed to the diagnosis of migraine by International Headache Society criteria. Baseline pain was of moderate to severe intensity. We extracted dichotomous data for the primary outcome measure of headache response (a successful outcome) at two hours. This was defined as a reduction of pain from moderate or severe to mild or none.

Search Results

We found RCTs and meta-analyses of seven treatments (counting effervescent aspirin and metoclopramide as different from non-effervescent):

- Sumatriptan
- Naratriptan
- Rizatriptan
- Zolmitriptan
- Excedrin (paracetamol 500 mg + aspirin 500 mg + caffeine 130 mg)
- Aspirin 900 mg with metoclopramide 10 mg (including an effervescent preparation)
- Tolfenamic acid.

References to all the papers found are given on the Internet version, or can be obtained from the ***Bandolier*** office. References to meta-analyses are given here.

Analysis

The analysis followed the path set out in the NNT insert. The outcomes were graphed onto L'Abbé plots, and the combined data for any dose of drug were used to calculate the number needed to treat.

Sumatriptan

The review by Tfelt-Hansen [1] pulled together information on nearly 7,500 patients entered into studies of subcutaneous, oral and intranasal sumatriptan. It looked at efficacy and adverse effects, with a prodigious searching strategy which included hand searches and interrogation of trialists and their industrial sponsors.

For 6 mg subcutaneous sumatriptan, data on 3,127 patients in 12 studies (Figure 1 upper panel) showed that 69% (1337/1927) of patients treated with subcutaneous sumatriptan had a successful result (decrease in headache severity from severe or moderate to none or mild) at one hour compared with 19% (226/1200) of those given placebo. This gave an NNT for success of 2.0 (95%CI 1.9 to 2.1) at one hour after injection.

For 100 mg oral sumatriptan, data on 2,890 patients in 12 studies (Figure 1 middle panel) showed that 58% (1067/1854) of patients treated with oral sumatriptan had a successful result at two hours compared with 25% (256/1036) of those given placebo. This gave an NNT of 3.0 (2.8 to 3.4).

For 20 mg intranasal sumatriptan, data on 1,420 patients in six studies (Figure 1 lower panel) showed that 61% (563/917) of patients treated with intranasal sumatriptan had a successful result at two hours compared with 30% (149/503) of those given placebo. This gave an NNT of 3.1 (2.7 to 3.8).

Naratriptan

Two studies with naratriptan were found, in which the main outcome was headache relief at four hours or later. Extrapolation from a graph on one of these (249 patients) was possi-

FIGURE 1: SUMATRIPTAN IN THE TREATMENT OF ACUTE MIGRAINE

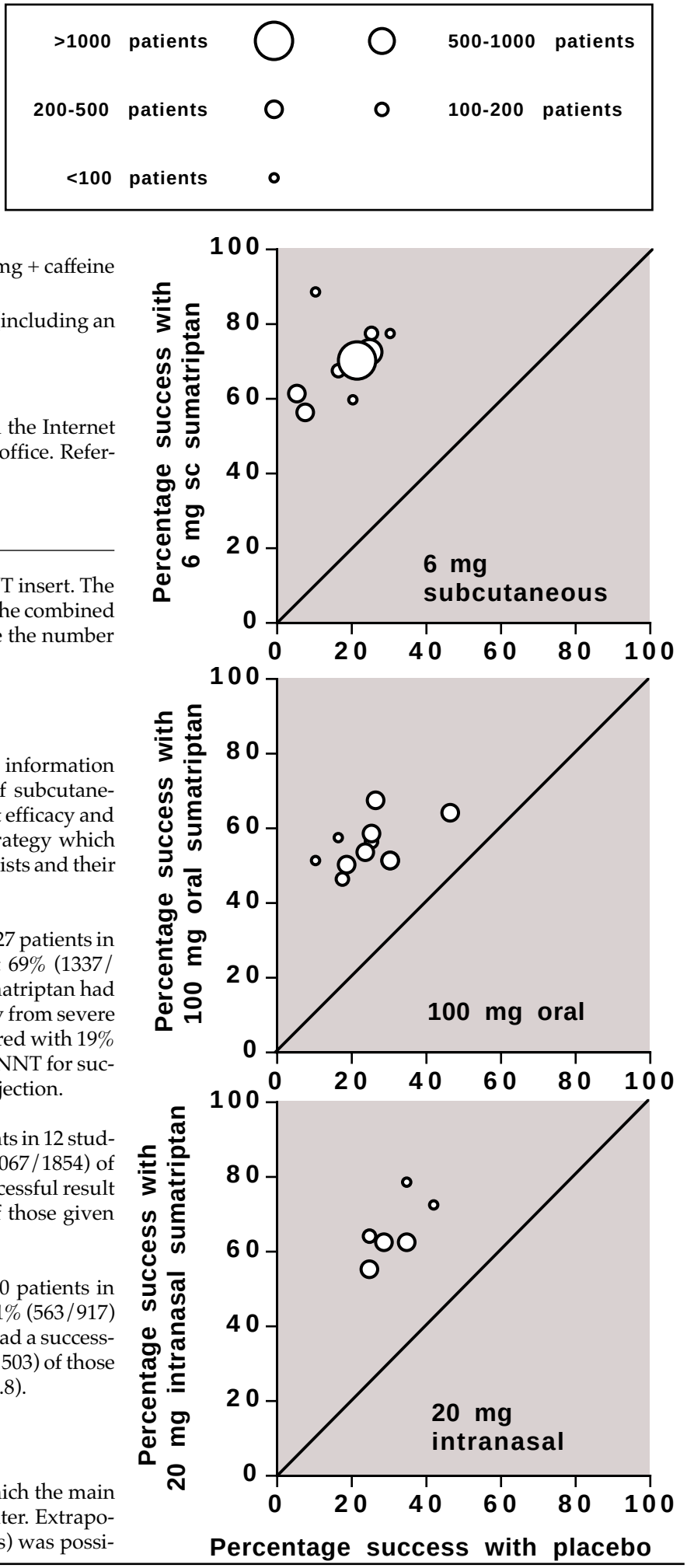


Table 1: Summary of randomised comparisons with placebo for pain relief at one or two hours (no pain or mild pain only)

Drug	Route	Time (hr)	Dose (mg)	Number of studies	Number of patients	NNT (95%CI)
Sumatriptan	Subcutaneous	1	6	12	3,127	2.0 (1.9 to 2.1)
Sumatriptan	Oral	2	100	12	2,890	3.0 (2.8 to 3.4)
Sumatriptan	Intranasal	2	20	6	1,420	3.1 (2.7 to 3.8)
Naratriptan	Oral	2	2.5	1	249	8.8 (4.3 to no benefit)
Rizatriptan	Oral	2	5	2	954	3.8 (3.1 to 4.9)
Rizatriptan	Oral	2	10	3	1,143	2.9 (2.5 to 3.5)
Zolmitriptan	Oral	2	2.5	2	651	3.5 (2.7 to 4.7)
Zolmitriptan	Oral	2	5	2	407	2.8 (2.2 to 3.9)
Zolmitriptan	Oral	2	10	1	369	3.1 (2.4 to 4.6)
Excedrin	Oral	2	500/500/130	3	1,220	3.9 (3.2 to 4.9)
Aspirin/metoclopramide	Oral	2	900/10	3	765	3.3 (2.7 to 4.2)
Tolfenamic acid	Oral	2	200	1	84	2.1 (1.5 to 3.5)

ble, and showed that 42% of patients treated with oral naratriptan had a successful result at two hours compared with 30% of those given placebo. This gave an NNT of 8.8 (95%CI 4.3 to no benefit).

Rizatriptan

Several studies on rizatriptan were obtained, most of which examined a variety of doses between 2.5 mg and 40 mg. Most information was available for the 5 and 10 mg doses.

For 5 mg oral rizatriptan, data on 954 patients in two studies showed that 58% of patients treated with 5 mg oral rizatriptan had a successful result at two hours compared with 32% of those given placebo. This gave an NNT for success of 3.8 (3.1 to 4.9) at two hours.

For 10 mg oral rizatriptan, data on 1143 patients in three studies showed that 64% of patients treated with 10 mg oral rizatriptan had a successful result at two hours compared with 29% of those given placebo. This gave an NNT for success of 2.9 (2.5 to 3.5) at two hours.

Zolmitriptan

A number studies on zolmitriptan were obtained, most of which examined a variety of doses between 1 mg and 25 mg. Most information was available for the 2.5 and 5 mg doses, and most came from a single study.

For 2.5 mg oral zolmitriptan, data on 651 patients in two studies showed that 64% of patients treated with 2.5 mg oral zolmitriptan had a successful result at two hours compared with 35% of those given placebo. This gave an NNT for success of 3.5 (2.7 to 4.7) at two hours.

For 5 mg oral zolmitriptan, data on 407 patients in two studies showed that 67% of patients treated with 5 mg oral zolmitriptan had a successful result at two hours compared with 31% of those given placebo. This gave an NNT for success of 2.8 (2.2 to 3.9) at two hours.

For 10 mg oral zolmitriptan, data on 369 patients in one study showed that 66% of patients treated with 10 mg oral zolmitriptan had a successful result at two hours compared with 34% of those given placebo. This gave an NNT for success of 3.1 (2.4 to 4.6) at two hours.

Excedrin (paracetamol 500 mg + aspirin 500 mg + caffeine 130 mg)

A review of three large studies [2] give results on a US over-the-counter migraine product called Excedrin Extra-Strength, consisting of paracetamol, aspirin and caffeine. This may not be available in the UK, but it is roughly equivalent to one paracetamol plus one aspirin taken with a strong cup of coffee (given that nausea is not too much of a problem).

Combining three similar studies with 1,220 patients, they found that 59% of patients had a successful result with Excedrin compared with 33% of those with placebo. The NNT was 3.9 (3.2 to 4.9).

Aspirin 900 mg with metoclopramide 10 mg

Three studies (including one with effervescent aspirin - Migravess) studied 765 patients. Combined they showed that 62% of patients had a successful result with aspirin/ metoclopramide compared with 31% in those with placebo. The NNT was 3.3 (2.7 to 4.2).

Tolfenamic acid

A single study with 84 patients compared tolfenamic acid rapid release 200 mg. In the placebo group 29% of patients had a success at two hours, compared with 77% with tolfenamic acid. This equated to an NNT of 2.1 (1.5 to 3.5).

Summary

Table 1 gives the number of trials and patients in each comparison, and NNT for each drug and dose analysed. Where there were at least two studies or at least 400 patients studied

a league table of NNTs (Figure 2) shows the relative efficacy of the oral antimigraine analgesics for successful treatment at one or two hours.

Comment

All this means that there is a lot of information out there on pharmacological treatments of acute migraine attacks. The great mass of evidence, on 7,500 patients, is for sumatriptan, and relatively little yet on the newer triptans. For some common treatments ***Bandolier*** could find no comparable data - reflecting perhaps the fact that some have been around for a long time. A paper with much wisdom [3] comments upon unpublished meta-analyses for some triptans.

Effectiveness is not the whole story, and adverse effects are often well reported. Tfelt-Hansen [1] analyses these for sumatriptan, but a much more detailed analysis of the event rates of individual adverse effects with the numbers needed to harm could be done.

Clearly this is a fertile area for more analysis, especially as a hatful of new triptans could be coming our way. Peter Goadsby's thoughtful paper [3] makes the case for the need for more treatments, for more analysis of those treatments, and for decisions of how to treat. Should we use a stepped approach (analgesic to ergots to triptans), or a stratified care model in which we analyse the severity of the problem and move immediately to the most appropriate care?

Goadsby also reminds us that "the natural history of a migraine attack is to stop. The use of four-hour time points has led to flatteringly high headache response data, which translate into unrealistic expectations for clinicians and disappointment for patients." The ideal end-point is the proportion of patients pain free at two-hours. So few studies give this endpoint that it is sidelined for now, especially for comparison with older studies.

Other issues

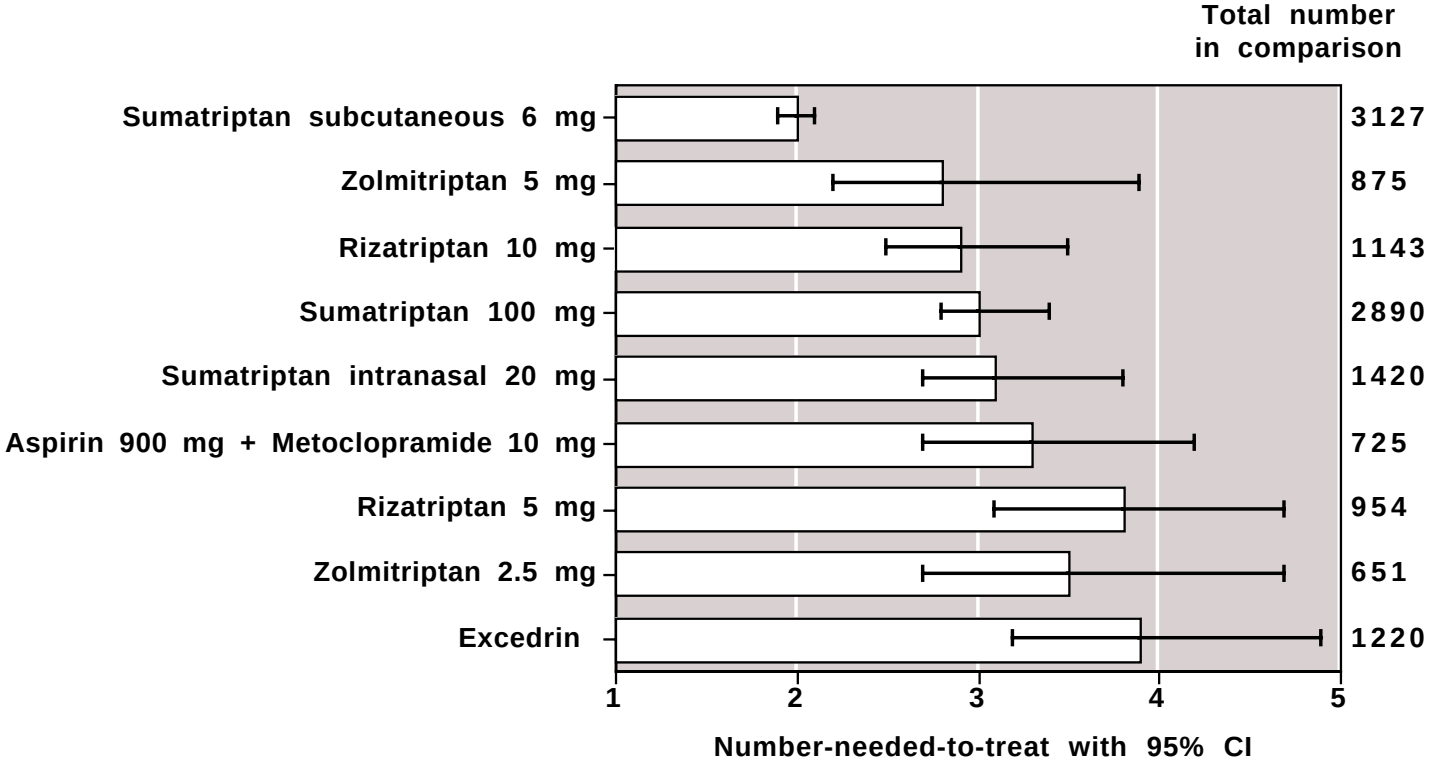
As well as stopping acute headache and adverse effects of medicines that do that, there are many other issues not touched on here. These include headache recurrence, and the whole issue of prophylactic measures for dealing with migraine.

Summarising information like this is no more than a snapshot. There is probably loads more information on newer treatments just waiting to be published, and as well as thanking pharmaceutical companies for sending information on their products, ***Bandolier*** invites them to send more information as it becomes available.

Then there is the issue of relative efficacy from indirect comparisons with placebo. Perhaps the gold standard is one enormous randomised trial with all the treatments examined head-to-head, but that's just baying for the moon. The point is that the information presents itself not like a boxing competition, with products knocking each other out, but like a sprint world record. As long as conditions are fair (same distance, no following wind), then the time the runner takes is the time the runner takes.

References are on page 7.

Figure 2: League table of number-needed-to-treat for successful treatment (moderate/severe to mild/no pain) of an acute migraine attack. Treatments were oral unless otherwise stated and at two hours except for subcutaneous sumatriptan, which was at one hour.



A LIGHT IN THE DARKNESS

One of the areas of health improvement which has been targeted in recent years is that of preventing injuries. A bulletin from R&D Wales [1] has gathered together a mass of evidence on injury prevention strategies and categorised it in terms of the strength of evidence and whether interventions are beneficial or harmful (http://www.uwcm.ac.uk/uwcm/lb/pep). ***Bandolier***'s eye was drawn to the question of the use of running lights on cars in daytime, and a meta-analysis [2] which might explain why all those Volvos and Saabs irritatingly have their lights on all the time.

Meta-analysis

This drew together all the known studies on the use of daytime running lights (DRL). Some of these were randomised (some cars had lights on, others did not, usually from a fleet of cars), some were before-and-after studies with a comparison group, and some were simple before-and-after studies, for instance when a new law came into force.

The distinction was drawn between the risk of accident for an individual car using DRL, and aggregate effects on the total number of accidents. The outcome was accidents occurring in daytime between cars, or between cars and pedestrians or cyclists. This makes sense, since at night-time all cars should have lights on, and use of DRL should make little difference for single-vehicle accidents.

Results

The design of studies seemed to make little difference on the magnitude of the reduction in accident rates for individual cars (Table 1). The estimate of the mean effect was about a 15% reduction in accident rates whether studies were randomised or not. There was also data showing that variability in accident rates between studies was found predominantly in small studies - only to be expected really - and that large studies gave consistent results.

There was also good agreement between the estimates of reduction in accident rates for different types of accidents, and overall, between individual car studies and those on aggregate effects of accidents (Table 2). The one point of disagreement was for rear-end collisions, where the aggregate data seemed to suggest a small increase while the individual car estimate was for a small decrease.

Table 1: Effect of study design on accident reduction rates

Study design	Percent reduction in accident rate (95% CI)
Randomised	15 (32 to +6)
Before-and-after with comparison group	18 (28 to 5)
Simple before-and-after design	14 (16 to 12)

The beneficial effects of DRL were maintained whether the proportion of cars using DRL was 30 or 50% at the start of a study, and from 60% to 95% at the end. There was a weak effect of latitude. Higher latitudes may mean more "low sun" conditions, or longer twilight, where DRL may be more effective at reducing accidents. Since the aggregate of about 15% reduction was across all latitudes, it might be that in the UK DRL could be slightly more effective than the average.

Comment

This is well done review, thoughtful, detailed and impressive. It makes a good case that using daytime running lights right now in the UK should reduce the effect of an accident for an individual car of about 15%. Accidents are not that uncommon, and this is an appreciable reduction. ***Bandolier*** has started using lights in the day.

There is also a lesson for public safety. In the UK there are many thousands of injuries caused by traffic accidents. Universal use of DRL could effect a reduction of perhaps 10%, with perhaps the same sort of reduction in death and injury. Simple 'back of stamp' economics would indicate that the cost of universal DRL in the UK might be a one-off £130 million for conversion (£5 per car at a service?), and trivial amounts thereafter. Putting that against a 10% reduction in road traffic deaths and injuries makes it an effective intervention whose cost may be offset by lower insurance premiums. Must ask the garage and the broker.

Table 2: Effects of DRL on accident rates for multiparty daytime accidents

Type of accident	Percent reduction in accident rate (95% CI)	
	Individual car	Aggregate estimate
Front or side impact	13 (16 to 10)	13 (14 to 12)
Rear end collision	16 (21 to 11)	+3 (0 to +6)
Pedestrian accident	25 (38 to 8)	20 (22 to 18)
Cyclist accident	no data	6 (9 to 4)
Motorcycle accident	no data	20 (23 to 18)
Type not stated	14 (20 to 7)	7 (9 to 4)
Mean of all types	14 (16 to 12)	12 (13 to 11)

References:

1 R Lyons et al. Injury Prevention. Health Evidence Bulletins Wales, September 1998.

2 R Elvik. A meta-analysis of studies concerning the safety effects of daytime running lights on cars. Accident Analysis and Prevention 1996 28: 685-94.

NAUSEA AND VOMITING IN EARLY PREGNANCY

In early pregnancy nausea affects up to 85% of women, and vomiting 50%. It doesn't happen just in the morning, nor in the first few weeks and months of pregnancy. Pregnant women lose time off work, and/or fail to deal with everyday activities. So treatments are important, and a recent Cochrane review gives us some answers about efficacy.

Search

This is a Cochrane review, so searching was exhaustive. Treatments tested for were different anti-histamine medicines, Pyridoxine (vitamin B6), the combination medicine Debendox, and P6 acupressure.

Results

There were three treatments with at least two trials, not all of which would be considered as properly randomised. Results were in many forms, but extractable as dichotomous outcomes was success judged as the absence of persistent nausea. For individual trials, the results are shown in the L'Abbé plot, and the pooled information is in the Table.

P6 acupressure in two studies showed 52% of patients with control having a success, compared with 75% with P6 acupressure. The NNT was 4.5 (3.2 to 7.5).

Debendox in three studies showed 49% of patients with control having a success, compared with 72% with Debendox. The NNT was 4.4 (2.9 to 9.1).

Pyridoxine in two studies showed 63% of patients with control having a success, compared with 65% with Pyridoxine. The NNT was 47 (8.6 to no benefit).

Comment

Pyridoxine doesn't seem to work, and Debendox was withdrawn because of fears (probably incorrect) of teratogenicity. That leaves P6 acupressure as the one treatment available with some evidence of efficacy.

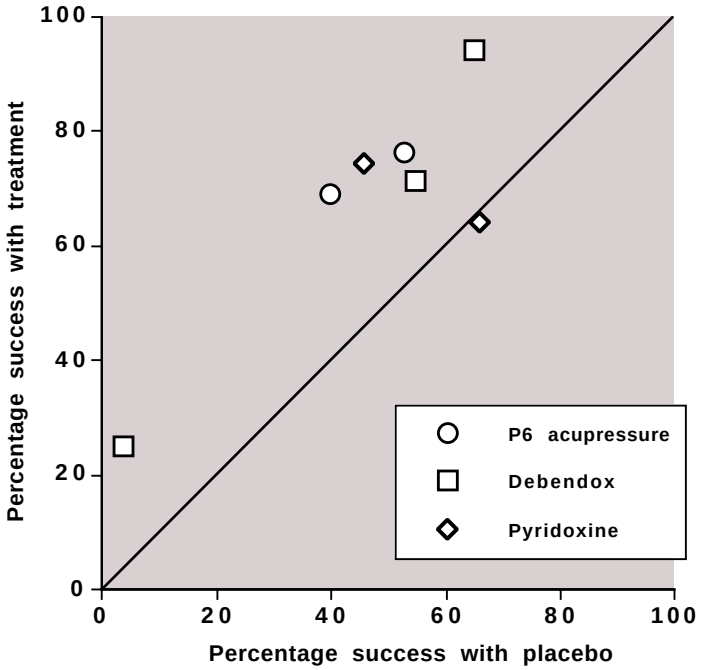
While there is more in the review than abstracted here, including some comments on adverse effects like drowsiness, the overwhelming feeling on reading it is how little evidence there seems to be for this important condition. Most of the 650,000 or so women delivering every year would appreciate more help. But the bottom line is that the success rate with control was consistently about 50% or so. Mostly the problem goes away.

Many thanks to the authors for sending original data to allow calculation of NNTs and the L'Abbé plot.

Reference:
1 D Jewell, G Young. Treatments for nausea and vomiting in early pregnancy. Cochrane Library 1998, 3rd issue. Date of most recent amendment 16 April 1998.

ISSN 1353-9906

Success rate (absence of persisting nausea in early pregnancy) with treatment and control



Summary of studies for treatment of nausea and vomiting in early pregnancy

Treatment	Number of studies	Number of patients	NNT (95%CI)
P6 acupressure	2	396	4.5 (3.2 to 7.8)
Debendox	3	240	4.4 (2.9 to 9.1)
Pyridoxine	2	392	47 (8.6 to no benefit)

Web watch

Finding good medical information electronically is fraught, as anyone who has surfed the Internet for a few minutes will know. Typing in some key words into a search engine like AltaVista produces hundreds or thousands of hits, but the quality of what is on offer is usually derisory. The power of the medium is degraded. What we need are gateways to information, knowledge and wisdom that can guarantee finding something of value. A number of these exist.

TRIP Database

One of ***Bandolier***'s favourites is the TRIP Database maintained by Jon Brassey in Gwent. This has been expanded to allow a search of 25 separate sites, through ***Bandolier*** to Cochrane, DARE and through to the Scottish Intercollegiate Guidelines Network. You might not like all the evidence you find, but it's a simple way in to evidence and information.

http://www.gwent.nhs.gov.uk/trip/test-search.html

Doctors Net

Doctors.net.uk is a medically-led, ethical company formed to facilitate improved patient care through modern medical communication and education. It is run by practising NHS doctors whose vision was to create a portal to medical resources on the Internet. It has been developed with the co-operation of every medical school in the UK, Medical Colleges, the Department of Health, the NHS and the various committees responsible for continuing medical education in the UK. Quality of information is a core principle and an educational/ethical committee has been formed to ensure the standards of information included in the site.

Doctors.net.uk gives every GMC registered doctor with a high-quality, professional Internet service as well as a free email address for life, personal web page, forums and discussion groups, a library and probably the cheapest bookshop on the web. To register - there is no charge - go to http://www.doctors.net.uk (you will need your GMC details). Try it out for a month or so using Name: visitor and Password: December (both case-sensitive).

Key components of the service are:

- Internet access and email
- Forums for discussion and debate (EBM forum already active)
- Online jobs service with personalised emailing
- Extensive range of library facilities
- Time-saving resources including a bookshop

Doctors desk

Another interesting site is doctors desk. Simon de Lusignan and his colleagues have created a place which gives some useful information. Worth watching as it grows.

http://drsdesk.sghms.ac.uk/notice.htm

Bandolier Conferences - Promoting Effectiveness in Health Care

The sixth ***Bandolier*** conference takes place on March 24th 1999 at the Royal College of Pathologists, 2 Carlton House Terrace, London SW1. The topic is "Stroke: what to do second. Optimising Secondary Prevention and Follow up Care."

Programme

9.30 Registration and coffee

10.00 Welcome:Andrew Moore-Editor of Bandolier

Chairman's introduction: Charles Forbes

10.10 *1st session; Where are we now, where do we want to go?*

Tony Snell: implementing effective care at the $1^0/2^0$ interface
Nick Hicks: perspectives from 1^0 care
Colin Baigent: evidence from anti-platelet trials

11.15 Coffee

11.30 *2nd session: Pharmacological interventions*

Charles Forbes: the clinician in a clinical trials set ting, the 2nd ESPS
Martin Duerden: view from the National Prescrib ing Centre
Tom Dent: option appraisals
Ceri Phillips: economic appraisals

1.00 Lunch

2.00 *3rd session: Non-pharmaceutical interventions*

Peter Langhorne: the contribution of stroke units
Ruth Empson: rehabilitation in the community
Ben Jabuni: role of the Stroke Association

3.15 Discussion, arguments, tea and depart.

For more information and registration form please fax Eileen Neail on 01865 226978.

Continued from page 4

References:

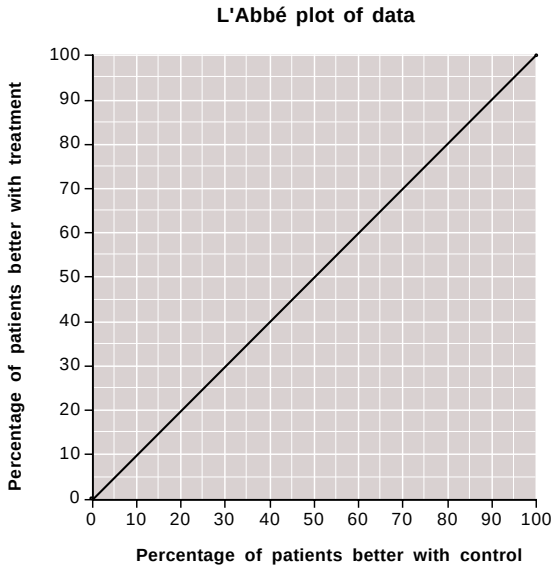
1 P Tfelt-Hansen. Efficacy and adverse events of subcutaneous, oral, and intranasal sumatriptan used for migraine treatment. A systematic review based on number needed to treat. Cephalaglia 1998 18: 532-8.
2 RB Lipton, WF Stewart, RE Ryan et al. Efficacy and safety of acetaminophen, aspirin and caffeine in alleviating migraine headache pain. Archives of Neurology 1998 55: 210-17.
3 PJ Goadsby. A triptan too far? Journal of Neurology, Neurosurgery, and Psychiatry 1998 64: 143-7.

Bandolier's NNT worksheet

A number needed to treat (NNT) is defined by a number of characteristics. This worksheet is designed as an aide memoir for working out NNTs from papers and systematic reviews. First fill in the answers to the questions, where appropriate, graph the data on the L'Abbé plot, and finally do the NNT calculation.

	Question/Action	Answer
A	What is the intervention (ie drug dose & frequency)?	
B	What is the intervention for?	
C	What is the successful outcome (and when or over what time did it occur)?	
D	How many had the intervention?	
E	How many had successful outcome with the intervention?	
F	Express this as a percentage (100 x E/D) and as a proportion (E/D)	
G	What is the control or comparator?	
H	How many people had the control?	
I	How many had successful outcome with the control?	
J	Express this as a percentage (100 x I/H) and as a proportion (I/H)	

Now graph the percentages for the trial on the graph from the ***percentages*** from F and J. This can be done for different outcomes of a trial, or individual trials in a systematic review or meta-analysis.



Now calculate the NNT using the ***proportions*** from F and J.

$$\text{NNT} = \frac{1}{\boxed{F} - \boxed{J}} = \frac{1}{\boxed{} - \boxed{}}$$

$$\text{NNT} = \frac{1}{\boxed{}} = \boxed{}$$